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<p>(54) Title: COMPOSITIONS USEFUL AS CONTRACEPTIVES IN MALES</p> <p>(57) Abstract</p> <p>A method of effecting contraception in human males comprises administering a combination of melatonin and an androgenic hormone in a contraceptively effective amount. Optionally, the melatonin and androgenic hormone can be further combined with a progesterone. The administration of melatonin and androgenic hormone also provides a method of preventing prostate cancer in men.</p>		

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## COMPOSITIONS USEFUL AS CONTRACEPTIVES IN MALES

### Field of the Invention

5 This invention relates to compositions useful as contraceptive agents in human males. More specifically, the invention relates to compositions comprising a contraceptively effective amount of a combination of melatonin and an androgenic hormone.

### Background of the Invention

10 The majority of methods for effecting contraception available to humans today are practiced by females. In addition to various physical and chemical barriers to sperm transport that women can use, such as vaginal foams, diaphragms and intrauterine devices, a number of oral contraceptives comprising steroidal  
15 hormones, typically a combination of a progestogen and an estrogen, have been developed. Men who wish to assume the responsibility for preventing conception have had fewer options. At present, there are only two widely acceptable methods for the human male, the  
20 condom and the vasectomy, and there are drawbacks associated with each of these methods. The failure rate with condoms can be high, resulting in unwanted pregnancies. Vasectomies, for all practical purposes, must be considered irreversible, although limited  
25 progress has been made in recent years in reversing vasectomies.

A number of efforts have been made to find a safe, effective, hormone- (or other chemical-) based reversible contraceptive for males, but to date they have met with little success. Most known  
5 antispermatogenic agents cannot be used in the development of a male contraceptive because they have been found to be nonspecific cytotoxic agents, mutagenic, carcinogenic and/or exhibit deleterious side effects.

10 For example, androgens, such as testosterone, have been studied. Exogenous testosterone is known to suppress gonadotropin production and thus inhibit both leutinizing hormone (LH) and follicle stimulating hormone (FSH). Normal blood levels of both of these  
15 hormones are required for spermatogenesis. In a 1972 study, daily injections of testosterone propionate over a 2-3 month period were shown to produce azoospermia (i.e., a level of sperm production below that required for the fertilization of a female) with  
20 no decrease in libido or potency and with a return to normal sperm count within five months after the administration was stopped. Reddy, P.R. and J.M. Rao, Contraception 5:295 (1972). To suppress spermatogenesis, however, serum levels of testosterone  
25 had to be greater than those normally found, thereby possibly subjecting the user to adverse effects of excessive testosterone, including increased red cell mass, water retention, increases in serum cholesterol and hypertension. Liver toxicity and carcinogenicity  
30 also can be complications of high dosage administration of these compounds. Henderson, J.T., et al. Lancet 1:934 (1971).

In another study, the effectiveness of testosterone oenanthate was found to be dependent upon

the frequency of administration, with optimal results occurring with weekly intramuscular injections of 200 mg. See Wu, F.C.W., Clinical Endocrin. 29:443 (1988). At that dosage level and frequency of administration, only 50% of the subjects tested achieved azoospermia, while 40% became oligospermic (i.e., sperm counts under five million/ml) after 10 weeks of treatment. The testosterone administration was found to be ineffective as a contraceptive in the remaining 10% of the men. Recovery of fertility was found to take six months or more. In addition, side effects included weight gain and gynecomastia. Decreasing the frequency of administration even at increased dose levels was found to result in a loss of suppression. Orally effective androgens, such as testosterone undecanoate, given in supraphysiological doses also have been found to be ineffective. See, Nieschlag, E. et al., Contraception 18:607 (1978).

Combinations of androgens and progestogens also have been administered in hopes of seeking more effective gonadotropin suppression by the synergistic action of the two types of hormones. The major finding from this study was that azoospermia could be induced in only a portion of the subjects tested even when relatively high doses were administered. Shearer, S.B., et al. Intl. J. Androl. supp. 2:680 (1978). In another study, a combination of daily oral administration of medroxy-progesterone acetate and percutaneous testosterone cream was found to be ineffective for achieving widespread azoospermia.

Antiandrogens having progestational effects also have been tested as possible contraceptive agents. Although some have been shown to suppress gonadotropins, studies have indicated that their

administration can cause a significant loss of libido and sexual potency. Bremner, W.J. and David De Kretser, The New England J. of Med. 295(20):1111 (1976).

5           A variety of other agents also have been examined as possible contraceptive agents without success, including antineoplastic drugs, nitrofurans, thiophenes and dinitropyrroles. Antineoplastic drugs are known to be toxic to sperm production, but no  
10       drugs within this class have been found which inhibit spermatogenesis at a dosage that also is not toxic to other tissues. The other types of compounds listed above were shown in studies to have unacceptable toxicities in other organ systems and have not been  
15       used in human trials. Bremner and De Kretser, Id.

          Attempts to use estrogen as a contraceptive for males also have failed, as side effects associated with its administration include gynecomastia and libido loss. Marcus, R. and S.G. Koreman Ann. Rev. Med. 27:357 (1976). Another effort to develop a male  
20       contraceptive involved the use of gossypol, a phenolic compound extracted from cotton plants, but it was found that this substance caused severe hypokalemia and weakness as well as diarrhea, edema, dyspnea,  
25       neuritis and other toxic effects. Lawrence, S.U., A. M. Phar. 21:57 (1981).

          Accordingly, it is a principal object of this invention to provide a contraceptive composition for men which will reliably cause azoospermia, is safe,  
30       reversible, easily administered and acceptable to potential users. It is a further object of this invention to provide such a contraceptive which will not impair virility, potency or androgen aspects of metabolism.

### Summary of the Invention

In accordance with the present invention, there is disclosed a method for effecting contraception in human males desiring such effect which comprises administering a combination of melatonin and an androgen in dosages effective to effect contraception. Optionally, the melatonin and androgen can be administered in further combination with a progestogen. In a preferred embodiment, the contraceptives of this invention are administered in oral dosage form. In accordance with the present invention, there also is disclosed a method for preventing cancer in human males by administering effective dosages of melatonin.

### Detailed Description of the Invention

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized and secreted by the pineal gland. The exact role of the hormone has not yet been determined. Exogenous melatonin administration in humans has been studied in conjunction with a hypothesis that an abnormal melatonin rhythm is associated with endogenous depression and for pharmacokinetic purposes (Waldhauser, F., Neuroendocrinology 39:307, 313 [1984]) and in connection with sleep-wake rhythms and the phenomenon of "jet-lag" following airplane trips associated with a change in time zones.

Researchers also have investigated the effects of exogenous melatonin administration on the gonads of various animal species. Female rats injected with

melatonin at certain times of the day showed an inhibition of ovulation. Studies also showed that the injection of melatonin into female Syrian golden hamsters had an inhibitory effect on the gonads and on ovulation. Similar effects, however, were not shown in other female mammalian species injected with melatonin. Specifically, the administration of melatonin to sheep (Kenneway, D.J. et al., J. Reproductive Fertility 73:859 [1985]) and to primates (Reppert, S.M., et al., Endocrin. 104:295 [1979]) did not result in a direct alteration of their reproductive physiology.

Recently, it has been discovered that pharmacological doses of melatonin administered daily to a human female selectively suppress the normal mid-menstrual cycle surge in LH sufficient to prevent ovulation and thus can be used as an effective contraceptive for human females. See U.S. Patent Number 4,855,305, filed March 23, 1987.

The effects of melatonin administration to male animals also have been studied. The injection of melatonin into male Syrian golden hamsters at certain specific times of the day was found to have an inhibitory effect on the development of the gonads, spermatogenesis and the weight of the testes. In several studies with male rodents, however, melatonin administration was shown to have only a transitory effect on the testes and their ability to produce sperm. If the melatonin was administered on a continuous basis for an extended period of time, the sexual organs in the male rodents became refractory and spermatogenesis resumed, even if the doses of exogenous melatonin were increased. See, for example, Reiter, R.J. Proc. Soc. Exp. Biol. Med. 163:264

(1980); Reiter, R.J. Endocrin. Rev. 1:109 (1980).

5 The present invention is based on the discovery  
that pharmacological doses of melatonin administered  
daily in combination with an androgen to a human male  
substantially inhibit the production of LH and FSH and  
thereby decrease sperm production sufficient to  
achieve azoospermia. The present invention is  
directed to a method of effecting contraception in a  
human male by daily administering to the male a  
10 combination of melatonin and an androgen in  
contraceptively effective dosages. For purposes of  
this application, "contraceptively effective dosages"  
are dosages which inhibit spermatogenesis sufficiently  
to induce azoospermia.

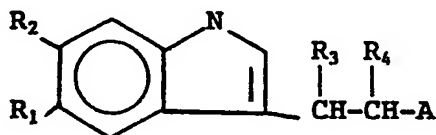
15 The present invention also is directed to a  
method of preventing prostate cancer and other  
malignant diseases that affect the male sexual organs.

In accordance with this invention, melatonin and  
a selected androgen are administered in dosages  
20 sufficient to suppress the user's normal production of  
leutinizing and follicle stimulating hormones so as to  
decrease sperm production below that required for the  
fertilization of a female. Generally, the melatonin  
is administered in amounts ranging between about 2 mg  
25 and about 2000 mg per day. Preferably about 25 mg to  
about 200 mg melatonin are administered daily. It may  
be advantageous, although certainly is not required,  
to initially administer the melatonin at relatively  
high dosages within this general range until  
30 azoospermia is achieved, which can take several weeks.  
Then, the melatonin can be administered at relatively  
lower dosages sufficient to maintain azoospermia.

As used herein, the term melatonin also  
encompasses melatonin analogs which have a

contraceptive effect when administered to human males in combination with an androgen. Such melatonin analogs can have the general formula:

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wherein  $R_1$ ,  $R_3$  and  $R_4$ , individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms,  $R_2$  is selected from hydrogen, hydroxy or an alkoxy group having from 1 to about 4 carbon atoms, and A is selected from the group consisting of -OH or -NH-CO- $R_5$ , wherein  $R_5$  is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is -NH-CO- $R_5$ , and  $R_1$  and  $R_5$  are both methyl and  $R_2$  is hydrogen, both of  $R_3$  and  $R_4$  are not hydrogen. Preferred compounds are those in which  $R_2$  is hydrogen or methoxy, with hydrogen being most preferred. Melatonin analogs encompassed within this definition include N-acetyl serotonin, N-acetyl, 5-hydroxy, 6-methoxytryptamine, 6-hydroxy-melatonin, 5-hydroxytryptophol and 5-methoxy tryptophol, with N-acetyl serotonin being preferred.

The melatonin is administered in combination with an androgen. Suitable androgens include testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyl testosterone, fluoxymesterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol and testolactone. Other male androgens may also be suitable. The androgen generally is administered in daily doses of about 1 mg to about 400

mg. If the androgen used is testosterone, preferred dosages range from about 1.5 mg to about 7.5 mg per day. Preferred dosages of other androgens can be calculated on the basis of their potency relative to that of testosterone. By administering the androgen in combination with melatonin, the dosages of androgen necessary to suppress the levels of sperm production so as to achieve azoospermia are less than those that are needed when the androgen has been tried as the single active component of a male contraceptive. The decreased dosage of androgen is beneficial, as it avoids the problems of depression of libido and potency and the undesirable side effects of excess androgen administration that have been observed in the past. The actual amount of the androgen provided in each daily dose will depend upon the particular androgen chosen, its relative potency, and the method of administration selected. For example, a lesser quantity of a more potent androgen may achieve the same results as a larger quantity of a less potent androgen.

The melatonin and selected androgen conveniently can be combined and administered together, although, if desired, they can be administered separately. The melatonin and androgen can be administered orally, parenterally, by way of depot injection or in the form of an implant. If desired, the melatonin can be administered orally and the androgen can be administered in the form of a depot or vice versa. Administration is most convenient when the hormones are in oral dosage form, such as capsules, tablets, suspensions or solutions. Capsules or tablets are preferred. Capsules can be prepared by mixing the compound with a pharmaceutically-acceptable excipient

and then filling gelatin capsules with the mixtur in accordance with conventional procedures.

Alternatively, the hormones can be mixed with one or more lubricants, such as stearic acid or magnesium stearate, flavor ameliorating agents, disintegrating elements, including potato starch and alginic acid, binders, such as gelatin and corn starch, and/or tablet bases including lactose, corn starch and sucrose, and then pressed into tablets.

As an alternative to oral administration, the hormones can be administered parenterally or in the form of a solid implant. For parenteral administration, the hormones are provided in injectable doses of a solution or suspension of the hormones in a physiologically acceptable diluent with a pharmaceutical carrier. The carrier can comprise water or an oil and optionally can contain a surfactant or other pharmaceutically acceptable adjuvant. Suitable oils include those of animal, vegetable, petroleum or synthetic origin, including peanut, soybean, corn, sesame, castor and mineral oil. Preferred liquid carriers include water, saline, aqueous sugar solutions and glycols such as propylene glycol or polyethylene glycol. Desirably, such injectable formulations are provided for intramuscular depot injections.

The hormones also can be administered in the form of an implant, which is formulated such that it will provide a sustained release of the melatonin over time. To make the implant, the hormones can be compressed into small cylinders and placed inside a physiologically acceptable shell material such as a biodegradable or porous polymer in accordance with conventional implant technology.

In a preferred embodiment of this invention, the contraceptive compositions are administered in oral dosage form, preferably in the form of pills or capsules. The pills or capsules can be packaged in

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any manner suitable for delivery and use. Conveniently, they can be packaged in the form of a pharmaceutical kit or package similar to those conventionally used for oral contraceptives for women in which the daily unit dosage forms are provided or

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arranged in a contiguous, sequential order which will enable the man taking the pills to take the proper formulation on any given day. Suitable kits or packages include the conventional bubble package containing individual bubbles for a selected number of days in a sheet of flexible plastic. The bubbles are sealed by a sheet of plastic which can break and release a pill when the bubble is pressed. On the first day of medication, the first pill in the sequence is removed from its individual slot and

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taken. The next pill in the sequence is taken the next day and so on thereafter until the dispenser is empty. Appropriate notations or instructions can be placed on the dispensing kit to guide or instruct the user in the proper use of oral contraceptives.

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In a preferred embodiment of this invention, the melatonin and androgen are administered in further combination with a progestogen. Efficiency of spermatogenesis is dependent upon GnRH and the LH pulses. The GnRH is affected by the administration of

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progestogens. Melatonin amplifies the effect of the progestogens such that smaller quantities of progestogen can be used to impact spermatogenesis than otherwise would be sufficient. Any progestationally active compound is suitable for use as the progestogen

component of the present invention. Suitable progestogens include progesterone and derivatives thereof. The presently preferred progestogen is norethindrone (i.e., 19-nor-17 $\alpha$ -ethynyl-17 $\beta$ -hydroxy-4-androsten-3-one) and norgestrel (13 $\beta$ -ethyl-17 $\alpha$ -ethynyl-17 $\beta$ -hydroxygon-4-en-3-one). Other progestogens include the chlormadinone-acetate (6-chloro-17-hydroxy-pregna-4,6-diene-3,20-dione acetate), norethynodrel (17 $\alpha$ -ethynyl-17-hydroxy-estr-5(10)-en), medroxyprogesterone acetate (17 $\alpha$ -acetoxy-6 $\alpha$ -methyl-pregn-4-ene-3,20-dione), megestrol acetate (17 $\alpha$ -acetoxy-6-methyl-pregna-4,6-diene-3,20-dione), lynestrenol (17 $\alpha$ -ethynyl-17 $\beta$ -hydroxy-estr-4-ene), quingestrone (3-cyclopentyloxy-pregna-3,5-diene-20-one), norethindrone acetate (17 $\beta$ -acetoxy-17 $\alpha$ -ethynyl-estr-4-en-3-on), ethynodiol acetate (3 $\beta$ ,17 $\beta$ -diacetoxy-17 $\alpha$ -ethynyl-estr-4-ene), dimethisterone [17 $\beta$ -hydroxy-6 $\alpha$ -methyl-17(-1-propynyl)-androst-4-en-3-one], and levonorgestrel.

The progestogen is administered in the range of about 10  $\mu$ g to about 1 mg per day, preferably in the range of about 30  $\mu$ g to about 150  $\mu$ g per day. As with the androgen component of the contraceptives of this invention, the actual amount of progestogen provided in each daily dosage depends upon the particular progestogen chosen, its relative potency and the method of administration selected, with lower doses typically needed for administration of an implant or injection than for oral administration.

In this embodiment of the invention, the three active components conveniently can be combined and administered together, although they also can be administered separately.

Alternativ ly, if desired, an estrogen can be administered in place of the progestogen. Suitable estrogens include ethinyl estradiol (i.e. 17 $\alpha$ -ethynyl-3,17 $\beta$ -dihydroxy-estra-1,3,5(10)-triene) and mestranol (17 $\alpha$ -ethynyl-17 $\beta$ -hydroxy-3-methoxy-estra-1,3,5(10)triene). Other suitable estrogens include estradiol (3,17 $\beta$ -dihydroxy-estra-1,3,5(10)-triene), estradiol(3,-16 $\alpha$ ,17 $\beta$ -trihydroxy-estera-1,3,5(10)-triene, estrone (3,hydroxy-estra-1,3,5(10)-triene-17-one), diethylstilbestrol, quinestradiol (3-cyclopentyloxy-16 $\alpha$ ,17 $\beta$ -dihydroxy-estra-1,3,5-(10)-triene) and estrone sulfate. Typically, they can be administered in dosages ranging from about 2  $\mu$ g to about 100  $\mu$ g per day; preferably in dosages ranging from about 10  $\mu$ g to about 50  $\mu$ g per day.

A number of regimens are suitable for administering the combination of melatonin, androgen and progestogen (or estrogen). In one embodiment, the melatonin and androgen are administered every day on a continuous basis. If desired, the dosage can be relatively high until azoospermia has been achieved, then lesser quantities may be sufficient to maintain the condition. For example, in one regimen, a combination of about 500 to about 1200 mg of melatonin and about 100 mg to about 300 mg androgen is administered by means of an intramuscular depot injection on a weekly basis until azoospermia is achieved. If a progestogen also is included in the formulation, it typically can be provided in dosages of about 500  $\mu$ g to about 1 mg. Then, to maintain the condition, it may be possible to either increase the length of time between injections or decrease the concentration of each hormone in the preparation. If desired, once azoospermia has been achieved, the

hormones can be administered conveniently on a maintenance basis in oral form.

In an alternative embodiment, the melatonin and androgen are administered solely in oral dosage form. With daily oral administration, lesser amounts of the hormones typically are needed than when administration is by injection. In one regimen, the melatonin is administered in dosages of about 50 mg to about 150 mg per day and the androgen is administered in dosages of about 20 mg to about 50 mg per day on a continuous daily basis. If the regimen further comprises a progestogen, the progestogen typically is administered in dosages of about 100 µg to about 400 µg per day. Other useful regimens can be determined using routine experimentation by those with ordinary skill in the art, taking into consideration a particular patient's physiology, the method of administration he prefers and the specific androgen selected for administration.

As noted above, it also has been discovered that the administration of melatonin and an androgen in the amounts disclosed above can be effective in preventing prostate cancer and other forms of cancer that affect the sexual organs and accessory sexual organs of the human male. This discovery provides an important benefit to human males who take the compositions of this invention as a contraceptive. The melatonin and androgen are administered in dosages sufficient to prevent or significantly reduce the risks of getting cancer. Generally, the melatonin and androgen are administered in the general dosages and regimens set forth above.

The present invention is further described and illustrated by the following examples, which are provided for informational purposes and are not to be

construed as unduly limiting the scope of the invention.

Example I

5 A twenty-three year old male is administered a depot injection of 1000 mg melatonin and 200 mg testosterone oenanthate on a weekly basis. The patient becomes azoospermic and contraceptive efficacy is achieved. The injections are continued to maintain azoospermia.

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Example II

A thirty-five year old man is administered a pill on a daily basis which comprises 75 mg/day melatonin, 40 mg/day androgen and 1 mg/day progestogen. Contraceptive effects are achieved after 4 weeks.

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Example III

A combination of 7.5 mg melatonin, 30 mg 19-nortestosterone, and 100 µg progestogen is administered in a depot preparation intramuscularly. Azoospermia is achieved after 30 days. At the end of  
20 four years of monthly injections the medication is stopped and spermatogenesis resumes.

Example IV

A combination of 200 mg testosterone oenanthate and 5000 mg melatonin is administered to a thirty two  
25 year old man on a weekly basis by means of a depot injection until azoospermia is achieved (one month). The patient now continues medication with a combination of 75 mg melatonin and 40 mg testosterone oenanthate in tablet form on a daily basis to maintain  
30 azoospermia.

Example V

A twenty nine year old man is medicated with a depot injection of melatonin (5000 mg) and testosterone propionate (200 mg) on a weekly basis for three weeks until azoospermia is achieved. The patient then continues a daily oral preparation of methyl testosterone (10 mg) and melatonin (75 mg) for continuous administration to maintain azoospermia and effective contraception.

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Example VI

A forty-one year old man seeking contraceptive medication is started on a combination pill daily intake of methyl testosterone and melatonin in dosage ratios of 25 mg and 75 mg, respectively. He is checked on a weekly basis until azoospermia has been induced. During the induction period the patient uses alternative forms of contraception. When azoospermia has been determined (after a period of two to four weeks) he continues the daily medication and relies on the medication as a contraceptive.

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Example VII

A twenty-five year old man seeks contraceptive therapy but does not want to take daily medication or frequent injections. He is given a subdermal implant which comprises a mixture of testosterone propionate, melatonin and norethindrone for slow release. The dosages are calculated to produce supraphysiological levels of melatonin and testosterone and therapeutic levels of norethindrone. Medication capsules are kept in place (subdermally) for six years. When the client wishes to resume fertility the capsules are removed by

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means of a simple surgical incision and capsule withdrawal.

Example VIII

5 A twenty six year old man is started on oral  
medication with a combination pill containing 150 mg  
melatonin, 10 mg methyl-testosterone and 150 µg  
norethindrone. This combination pill is taken twice a  
day by the patient, once in the morning and once at  
night before retiring. The pills are taken on a  
10 continuous basis.

Example IX

15 A twenty seven year old man is prescribed an oral  
contraceptive which contains 75 mg melatonin, 25 mg  
methyl testosterone and 300 µg norethindrone per day.  
The combination pill is administered on a daily basis  
and sperm checks are instituted on a weekly basis.  
Azoospermia is achieved during the sixth week of  
medication. The medication is continued on a daily  
basis as an effective contraceptive.

Claims

1. A method of effecting contraception which comprises administering a combination of melatonin and an androgen in a series of daily doses to a human male desirous of effecting contraception at dose levels  
5 sufficient to induce azoospermia.
2. A method in accordance with claim 1, wherein the dosage level of melatonin ranges from about 2 mg to about 2000 mg per day of administration.
3. A method in accordance with claim 2, wherein the dosage level of melatonin ranges from about 25 mg to about 200 mg per day of administration.
4. A method in accordance with claim 1, wherein the androgen is selected from the group consisting of testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyl  
5 testosterone, fluoxymesterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol and testolactone.
5. A method in accordance with claim 4, wherein the dosage of androgen ranges from about 1 mg to about 400 mg per day of administration.
6. A method in accordance with claim 5, wherein the androgen is testosterone and the dosage level of the testosterone ranges from about 1.5 mg to about 7.5 mg per day of administration.
7. A method of effecting contraception in a human male which comprises administering a combination of melatonin, an androgen and a progestogen, in a series of daily doses at dose levels sufficient to  
5 induce azoospermia.

8. A method in accordance with claim 7, wherein the progestogen is selected from the group consisting of norethindrone, norgestrel, chlormadinone-acetate, norethynodrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, norethindrone acetate, ethynodiol acetate, dimethisterone, and levonorgestrel.

9. A method in accordance with claim 7, wherein the dosage level of melatonin ranges from about 2 mg to about 2000 mg per day of administration.

10. A method in accordance with claim 7, wherein the dosage of androgen ranges from about 1 mg to about 400 mg per day of administration.

11. A method in accordance with claim 8, wherein the dosage of progestogen ranges from about 10  $\mu$ g to about 1 mg per day of administration.

12. A method in accordance with claim 11, wherein the dosage level of progestogen ranges from about 30  $\mu$ g to about 150  $\mu$ g per day of administration.

13. A method of effecting contraception in a human male which comprises administering a combination of melatonin, an androgen and an estrogen, in a series of doses at dose levels sufficient to induce azoospermia.

14. A method in accordance with claim 13, wherein the estrogen is selected from the group consisting of ethinyl estradiol, mestranol, estradiol, estradiol estrone, diethylstilbestrol, quinestradiol and estrone sulfate.

15. A method in accordance with claim 13, wherein the dosage level of estrogen ranges from about 2  $\mu$ g to about 100  $\mu$ g per day of administration.

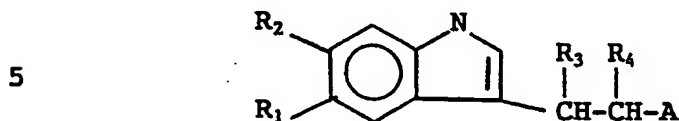
16. A method in accordance with claims 1, 7 or 13, wherein the method of administration is oral.

17. A method in accordance with claims 1, 7 or 13, wherein the method of administration is by parenteral injection in a physiologically suitable carrier.

18. A method in accordance with claims 1, 7 or 13 wherein the method of administration is by subcutaneous implant.

19. A method on accordance with claim 1, 7 or 13 wherein a melatonin analog having an azoospermia-inducing effect is administered in place of melatonin.

20. A method in accordance with claim 19, wherein the analog has the general formula



wherein  $R_1$ ,  $R_3$  and  $R_4$ , individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms.  $R_2$  is selected from hydrogen, hydroxy or an alkoxy group having from 1 to about 4 carbon atoms, and A is selected from the group consisting of -OH or -NH-CO- $R_5$ , wherein  $R_5$  is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is -NH-CO- $R_5$ , and  $R_1$  and  $R_5$  are both methyl and  $R_2$  is hydrogen, both of  $R_3$  and  $R_4$  are not hydrogen.

21. A composition for effecting contraception in a human male which comprises a contraceptively effective combination of melatonin and an androgen.

22. A composition in accordance with claim 21, wherein the androgen is selected from the group consisting of testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyl testosterone, fluoxymesterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone

decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol and testolactone.

23. A composition in accordance with claim 21, wherein the melatonin and androgen are provided in a series of daily doses, the dosage level of melatonin ranges from about 25 mg to about 200 mg per day of administration and the dosage level of androgen ranges from about 1 mg to about 400 mg per day of administration.

24. A composition in accordance with claim 21, wherein the melatonin and androgen are provided in a solution or suspension of a physiologically acceptable diluent with a pharmaceutical carrier.

25. A composition for effecting contraception in a human male which comprises a contraceptively effective combination of melatonin, an androgen and a progestogen.

26. A composition in accordance with claim 25, wherein the androgen is selected from the group consisting of testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyl testosterone, fluoxymesterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol and testolactone.

27. A composition in accordance with claim 25, wherein the progestogen is selected from the group consisting of norethindrone, norgestrel, chlormadinone-acetate, norethynodrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, norethindrone acetate, ethynodiol acetate, dimethisterone, and levonorgestrel.

28. A composition in accordance with claim 25, wherein the melatonin, androgen and progestogen are provided in a series of doses, the dosage level of melatonin ranges from about 25 mg to about 200 mg per day of administration, the dosage level of androgen ranges from about 1 mg to about 400 mg per day of administration and the dosage level of progestogen ranges from about 10 µg to about 1 mg per day of administration.

29. A composition in accordance with claim 25, wherein the melatonin and androgen are provided in a solution or suspension of a physiologically acceptable diluent with a pharmaceutical carrier.

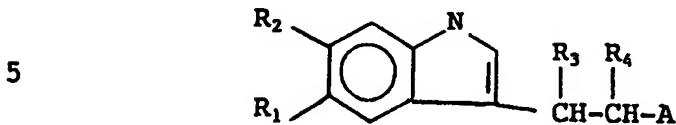
30. A composition for effecting contraception in a human male which comprises a contraceptively effective combination of melatonin, an androgen and an estrogen.

31. A compound in accordance with claim 30 wherein the estrogen is selected from the group consisting of ethinyl estradiol, mestranol, estradiol, estradiol estrone, diethylstilbestrol, quinestradiol and estrone sulfate.

32. A composition in accordance with claim 30, wherein the melatonin, androgen and estrogen are provided in a series of doses, the dosage level of melatonin ranges from about 25 mg to about 200 mg per day of administration, the dosage level of androgen ranges from about 1 mg to about 400 mg per day of administration and the dosage level of estrogen ranges from about 1 µg to about 100 µg per day of administration.

33. A composition in accordance with claim 21 or 25, wherein a melatonin analog having an azoospermia-inducing effect is administered in place of melatonin.

34. A composition in accordance with claim 33, wherein the analog has the general formula



10 wherein  $R_1$ ,  $R_3$  and  $R_4$ , individually, are hydrogen or an alkyl group having 1 to about 4 carbon atoms.  $R_2$  is selected from hydrogen, hydroxy or an alkoxy group having from 1 to about 4 carbon atoms, and A is selected from the group consisting of -OH or -NH-CO- $R_5$ , wherein  $R_5$  is either hydrogen or an alkyl group having from 1 to about 4 carbon atoms, provided that if A is -NH-CO- $R_5$ , and  $R_1$  and  $R_3$  are both methyl and  $R_2$  is hydrogen, both of  $R_3$  and  $R_4$  are not hydrogen.

35. A method of preventing prostate cancer in a human male which comprises administering in a series of dosages a combination of melatonin and an androgen in a prostate cancer-preventing amount.

36. A method in accordance with claim 35, wherein the dosage level of melatonin ranges from about 2 mg to about 2000 mg per day of administration.

37. A method in accordance with claim 35, wherein the androgen is selected from the group consisting of testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyl testosterone, fluoxymesterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol and testolactone.

38. A method in accordance with claim 37, wherein the dosage of androgen ranges from about 1 mg to about 400 mg per day of administration.

39. A method of preventing prostate cancer in a human male which comprises administering in a series of dosages a combination of melatonin, an androgen and a progestogen in prostate cancer-preventing amounts.

40. A method in accordance with claim 39, wherein the dosage level of melatonin ranges from about 2 mg to about 2000 mg per day of administration.

41. A method in accordance with claim 39, wherein the androgen is selected from the group consisting of testosterone, testosterone propionate, testosterone enanthate, testosterone cypionate, methyl testosterone, fluoxymesterone, danazol, dromostanolone propionate, ethylestrenol, methandriol, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol and testolactone.

42. A method in accordance with claim 41, wherein the dosage of androgen ranges from about 1 mg to about 400 mg per day of administration.

43. A method in accordance with claim 39, wherein the progestogen is selected from the group consisting of norethindrone, norgestrel, chlormadinone-acetate, norethynodrel, medroxyprogesterone acetate, megestrol acetate, lynestrenol, quingestrone, norethindrone acetate, ethynodiol acetate, dimethisterone, and levonorgestrel.

44. A method in accordance with claim 43, wherein the dosage level of progestogen ranges from about 10 µg to about 1 mg per day of administration.

45. A method of preventing prostate cancer in a human male which comprises administering in a series of dosages of a combination of melatonin, an androgen and a progestogen in prostate cancer-preventing amounts.

46. A dispensing package having oral contraceptives in unit dosage forms therein, said unit dosage forms adapted for oral administration of one unit dosage form daily and each unit dosage form
- 5 comprising about 2 mg to about 2000 mg melatonin and about 1 mg to about 400 mg of an androgen, said package comprising a unitary member having a desired number of individual storage pods formed therein, said
- 10 storage pods corresponding to the number of days during which said unit dosage forms are to be administered.


# INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 90/00090

<b>I. CLASSIFICATION F SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>5</sup> A 61 K 31/56, 31/565, 31/585, 31/57, 31/58, // IPC: (A 61 K 31/56, 31:40, 31:05), (A 61 K 31/565, 31:40, 31:05)		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC <sup>5</sup>	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	Chemical Abstracts, vol. 108, no. 19, 9 May 1988, (Columbus, Ohio, US), M.K. Vaughan et al.: "Influence of melatonin on the testicular regression induced by subcutaneous testosterone pellets in male rats kept in long or short photoperiod", see page 110, abstract no. 161875c, & J. Reprod. Fertil. 1988, 82(1), 277-84	1-34
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A	Chemical Abstracts, vol. 107, no. 19, 9 November 1987, (Columbus, Ohio, US), S. Daknin et al.: "Implantation of melatonin in mediobasal hypothalamus enhances the effect", see page 103, abstract no. 169223p, & Endocrinologia (Barcelona) 1987, 34(2), 42-5	1-34
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
8th October 1990	23.10.90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	R.J. Eernisse	

# INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 90/00090<sup>-2-</sup>

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>5</sup> (A 61 K 31/57, 31:40, 31:05, 31:565), (A 61 K 31/585, 31:40, 31:05, 31:565, 31:57), (A 61 K 31/58, 31:40, 31:05, 31:565, 31:57)		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
IPC <sup>5</sup>		
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>9</sup>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	Chemical Abstracts, vol. 103, no. 19, 5 March 1986, (Columbus, Ohio, US), L.K. Malendowicz: "Testosterone and melatonin effects on adrenal cortex of orchietomized and pinealectomized rats", see page 190, abstract no. 207248c, & Exp. Clin. Endocrinol. 1985, 85(3), 283-8 --	1-34
A	Chemical Abstracts, vol. 101, no. 5, 30 July 1984, (Columbus, Ohio, US), M. Rodriguez et al.: "Effect of pineal indoles and testosterone on sexual behavior in the rat", see page 97, abstract no. 33680d, & Rev. Esp. Fisiol. 1984, 40(1), 31-5 -- ./.	1-34
<p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
	23.10.90	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	R.J. Eernisse 	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, " with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, vol. 97, no. 23, 6 December 1982, (Columbus, Ohio, US), C.I. Sisk et al.: "Daily melatonin injection mimic the short day-induced increase in negative feedback effects of testosterone on gonadotropin secre- tion in hamsters", see page 111, abstract no. 193558x, & Biol. Reprod. 1982, 27(3), 602-8 --	1-34
A	Chemical Abstracts, vol. 87, no. 11, 12 September 1977, (Columbus, Ohio, US), R.H. Davis: "The effect of melatonin on the response to exogenous testosterone in mice", see page 85, abstract no. 78854x, & IRCS Med. Sci.: Libr. Compend. 1977, 5(6), 287 --	1-34
A	Chemical Abstracts, vol. 74, no. 13, 29 March 1971, (Columbus, Ohio, US), L. Debeljuk: "Effects of melatonin on changes induced by castration and testo- steron in sexual structures of male rats", see page 46, abstract no. 61260j, & Endocrinology 1970, 87(6), 1358-60 -----	1-34

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>1</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers ..... \* because they relate to subject matter not required to be searched by this Authority, namely:

\* Claims 35-45 See PCT-Rule 39.1(IV); Methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods.

2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>2</sup>

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.